The Six Diseases of WHO

Leprosy

M F R WATERS

Leprosy is the only bacterial disease included among the six selected for the United Nations Development Programme/World Bank/World Health Organisation's special programme for research and training in tropical diseases, and it alone has neither intermediate host nor significant animal reservoir or insect vector. It is a complex and chronic inflammatory disease of man, caused by the intracellular *Mycobacterium leprae*, which displays a wide clinical "spectrum" related to host ability to develop and sustain specific cell-mediated immunity. In high-resistant "tuberculoid" leprosy the localised signs are restricted to skin and nerves. Low-resistant "lepromatous" leprosy is a generalised disease affecting many systems, with widespread lesions of skin, peripheral nerves, upper respiratory tract, eyes, testes, and the reticuloendothelial system. The unstable intermediate part of the range is known as "borderline."

The spectrum concept of leprosy, with the modern five-group classification, was developed by Ridley and Jopling in 1962.^{1,2} It is based on immunological factors including the character of the host cell of the macrophage series (epithelioid in "polar" tuberculoid (TT), histiocytic in "polar" lepromatous (LL)), the number of lymphocytes (very numerous in TT, very scanty in LL), and the number of leprosy bacilli (very few in TT, and extremely numerous in LL). The lepromin skin test result is strongly positive in TT, negative in LL.

Clinical diagnosis

Clinical diagnosis rests on finding at least one of the following triad—anaesthesia, thickened peripheral nerves, and non-cultivable acid-fast bacilli in the skin lesions. In tuberculoid leprosy the skin lesions are single or very few, asymmetrical, dry, hypopigmented, and anaesthetic. They may be macules, plaques, or annular lesions, the last typically having sharp outer edges and narrow raised erythematous rims. A thickened sensory nerve may be felt running into the proximal part of a skin lesion. Sometimes a nearby nerve of predilection (ulnar above the elbow, median or superficial radial at the wrist, great auricular, lateral popliteal at the neck of the fibula, or posterior tibial at the ankle) may be thickened with or without functional damage. In borderline-tuberculoid leprosy several such nerves may be affected, and the skin lesions often exceed two or three. In borderline leprosy the lesions, though not symmetrical, are more numerous and tend to be dome shaped; if a skin lesion is annular the outer edge is flat and irregular, rising to a broad, thick, erythematous rim surrounding a small, sharp-edged, depressed, hypopigmented, anaesthetic centre. As one passes still further across the range, through borderline-lepromatous to lepromatous leprosy, the lesions become more and more

symmetrical and diffuse. In early cases the skin lesions are moist and not anaesthetic and are typically poorly defined macules, either hyperpigmented or hypopigmented, and papules and nodules. With time, the lepromatous skin becomes increasingly thickened and infiltrated, and the nerves of predilection become slowly and symmetrically thickened, although functional damage may take years to develop. Leprosy should be considered in the differential diagnosis of any patient who, having resided in the tropics or subtropics, develops chronic painless skin lesions or evidence of peripheral nerve damage.

Effect of drugs

In the past the disease was almost universally feared, both because all types could maim and deform and because lepromatous leprosy usually ran a chronic disfiguring course for many years before ending in death from secondary amyloidosis, laryngeal obstruction, or secondary infection. Although effective chemotherapy with the sulphone drugs was introduced in 1943, so that death from leprosy is now rare, the stigma is only slowly decreasing. It was hoped that the widespread distribution of dapsone, a very cheap and relatively non-toxic drug, would bring leprosy under control. It was found, however, that treatment had to be prolonged and is being given for about five years to patients with borderline-tuberculoid leprosy and for 20 years or preferably for life to patients with lepromatous leprosy. Even so, late relapse is often seen, especially in lepromatous and borderline-lepromatous leprosy, either because of drug-sensitive *M leprae* in patients who stop their treatment early from whatever cause (poor compliance is not unexpectedly a major problem) or because of the development of dapsone resistance, which may occur two³ to 24⁴ years or more after starting treatment. Moreover, further damage may occur after starting dapsone treatment owing either to more acute, immunologically mediated, inflammatory episodes ("reactions") or to injury to or secondary inflammation in the anaesthetic areas, especially of the hands and feet, which results from damage to the nerves.

Although Hansen recognised the leprosy bacillus in 1873, *M leprae*, which morphologically closely resembles *M tuberculosis*, has not yet been cultured in vitro. Experimental transmission was achieved only in 1960, when Shepard⁵ reported limited infection in mouse footpads. An inoculum of 5000 or 10 000 bacilli yields 10⁶ after about six months, but no increase occurs subsequently. During the log phase of multiplication the generation time is 12 to 13 days, the longest of any known bacterium. The footpad technique has been applied to studying the effect of drugs on the leprosy bacillus, the detection of dapsone resistance (first proved by Pettit and Rees in 1964⁶), and the immunology and pathogenesis of the disease. The time scale of such experiments is prolonged: standard dapsone sensitivity testing routinely takes six to 10 months. In 1967 Rees⁷ obtained lepromatous leprosy in thymectomised-irradiated mice. The latter appear exquisitely sensitive to *M leprae*, and have been used by Waters and Rees and their colleagues to detect the

National Institute for Medical Research and Hospital for Tropical Diseases, London

M F R WATERS, FRCP, FRCPATH, consultant leprologist

presence of the tiny numbers of persisting viable drug-sensitive bacilli found in treated lepromatous patients.⁸⁻¹⁰ Such "persisters" take many years to die out despite continuous chemotherapy, and are responsible for most of the relapses occurring in lepromatous patients who abscond from treatment after five, 10, or even more years.

Untreated lepromatous patients may excrete as many as 100m (10⁸) leprosy bacilli in 24 hours from the upper respiratory tract. Few bacilli are excreted through the intact skin, although many bacilli are present in the breast milk of untreated lepromatous mothers. Bacilli in dried nasal secretions may survive for from one to seven or more days in the shade or dark. Probably, therefore, the spread of *M leprae* closely resembles that of *M tuberculosis*, although authorities are divided in the absence of scientific proof over whether the main portal of entry of the leprosy bacillus is through the respiratory tract or through the skin. Family contacts of lepromatous patients may have ten times, and of tuberculoid patients twice, the incidence of leprosy compared with the general population, although this does not necessarily imply that tuberculoid leprosy is infectious. The incubation period is measured in years, being longer in lepromatous than tuberculoid leprosy. In leprosy-endemic areas the peak incidence occurs in those between 20 and 35 years of age. In a group of American servicemen sent to the tropics the incubation period for tuberculoid disease averaged four years and for the lepromatous 10 years.¹¹ Once dapsone treatment is started, leprosy bacilli from nasal washings¹² or from serial skin biopsy specimens of lepromatous patients¹³ fail to multiply in normal mice after about three to four months, indicating that a 99.9% kill is obtained in that period. A similar kill with clofazimine also takes about four months.¹⁴ Rifampicin, however, is rapidly bactericidal, achieving a 99.9% kill in three to four days.¹⁵⁻¹⁶ Therefore patients with lepromatous disease may very rapidly be rendered no significant public health risk. Nevertheless, the time scale of leprosy is unusually long, and in the chemotherapy of lepromatous leprosy one is observing a "slow-motion" response in an immunodeficient host. Even monotherapy with rifampicin fails to kill persisters, and rifampicin resistance has already been reported.¹⁷

Other scientific advances

Despite the disillusionment with dapsone as a cheap and simple means of controlling and eliminating leprosy, the period 1960-75 was one of considerable scientific advance. The accurate classification of patients resulted in much more precise clinical trials, and the concept of a spectrum proved a great stimulus to immunological studies. The application of the mouse footpad infection enabled bactericidal drugs to be identified and their rate of action and pharmacology to be studied, drug resistance to be confirmed, and persisters to be isolated. Nevertheless, in the absence of any routine source of *M leprae* other than skin biopsy specimens from untreated lepromatous patients, studies in the immunology of leprosy and biochemistry of *M leprae* were severely limited. BCG vaccination, although of considerable value in preventing early leprosy in Uganda, where the endemic was then declining, proved of little value in Burma or in Papua New Guinea.¹⁸ There was no specific skin test comparable with the Mantoux test in tuberculosis for studying the spread of *M leprae* through a community, even though Godal *et al*¹⁹ had reported a specific lymphocyte transformation test. Multidrug treatment, by analogy with tuberculosis the obvious way to prevent the further emergence of resistance to dapsone, had been little studied, partly because of the length of time necessary, and partly because of a decreasing supply of untreated lepromatous patients at some of the better equipped or more experienced centres.

In 1971 Kirchheimer and Storrs²⁰ reported that a proportion of normal nine-banded armadillos (*Dasypus novemcinctus*) developed lepromatous leprosy on inoculation with *M leprae*. It was soon obvious that, despite the difficulty of keeping armadillos

in captivity, infected animals could provide the large numbers of *M leprae* so urgently required for research. Therefore in 1974 the supply and distribution of armadillo-derived *M leprae* to workers undertaking agreed goal-orientated projects became organised by WHO in collaboration with scientists. In this way the Immunology of Leprosy (IMMLEP) Scientific Working Group came into being, acting as a model for the WHO Special Programme for Tropical Diseases, which was established in 1975. Considerable progress has been made in the development of a specific soluble skin test antigen for use in the recognition of subclinical infection. More complex lymphocyte transformation, leucocyte migration inhibition, and serological tests have also been developed.²¹ Draper²² has devised an elegant method of purifying *M leprae* almost free of host tissue without damaging bacillary antigens. This has enabled a vaccine to be developed consisting of irradiated, killed *M leprae* in combination with live BCG, which studies suggest may have the capacity to induce cell-mediated immunity in lepromin-negative contacts and patients with very early (indeterminate) leprosy—that is, acting as an immunotherapeutic agent.²¹ Protocols have been prepared concerning criteria for selection of trial areas and for the necessary pretrial studies. The scrupulous work gives grounds for quiet optimism. But the subject is complex, and, in view of the prolonged incubation period of leprosy, once the vaccination trial itself starts it may take at least a decade before adequate evaluation of the vaccine will be completed.

The Therapy of Leprosy (THELEP) Scientific Working Group and Steering Committee came into being in 1977. It has sponsored surveys for secondary dapsone resistance among treated patients with lepromatous and borderline-lepromatous leprosy in several countries, resistance to dapsone being detected wherever it has been sought.²³⁻²⁴ Surveys for primary dapsone resistance, which may occur in any type of leprosy, are now being set up. Scientists from developing countries have been trained in the technique of performing drug sensitivity tests on *M leprae* in mice. A major drug trial of multidrug treatment in untreated patients with lepromatous and borderline-lepromatous leprosy started in 1978 in two centres, one in South India, the other in Francophone Africa. Maximum regimens use daily doses for two years of three of the four bactericidal antileprosy drugs—rifampicin and dapsone, plus clofazimine in India and prothionamide in Mali. In the intermediate regimens combined chemotherapy is given for three months, whereas in the minimum regimen standard treatment with dapsone is augmented by a single 1500-mg dose of rifampicin. Patients are being monitored regularly for the presence of persisters. The results should indicate whether hopes for short-course chemotherapy, lasting from two to five years, are likely to be realised and which are the cheapest and most acceptable regimens for preventing resistance to dapsone. A protocol has also been developed for the multidrug treatment under field conditions of treated lepromatous and borderline-lepromatous patients; it is currently recommended that such patients should continue to take dapsone for a further 10 years after becoming skin-smear negative for leprosy bacilli,²⁵ and the trials about to start will investigate whether an "end phase" of intensive chemotherapy will allow this long period of consolidation treatment to be greatly shortened. A protocol is also being developed to investigate short-course chemotherapy in tuberculoid and borderline-tuberculoid patients.

Leprosy is the most chronic of all bacterial diseases. If hopes for control rest ultimately on the development of a vaccine, in the short and middle term—that is, for the next 20 years—improved chemotherapy is essential to prevent unnecessary suffering and to relieve the burden of prolonged and inadequate treatment on both patients and medical services alike.

References

- 1 Ridley DS, Jopling WH. A classification of leprosy for research purposes. *Lepr Rev* 1962;**33**:119-28.

- ² Ridley DS, Jopling WH. Classification of leprosy according to immunity: A five-group system. *Int J Lepr* 1966;**34**:255-73.
- ³ Pearson JMH, Haile GS, Barnetson RStC, Rees RJW. Dapsone-resistant leprosy in Ethiopia. *Lepr Rev* 1979;**50**:183-99.
- ⁴ Pearson JMH, Rees RJW, Waters MFR. Sulphone resistance in leprosy. A review of one hundred proven clinical cases. *Lancet* 1975;ii:69-72.
- ⁵ Shepard CC. The experimental disease that follows the injection of human leprosy bacilli into footpads of mice. *J Exp Med* 1960;**112**:445-54.
- ⁶ Pettit JHS, Rees RJW. Sulphone resistance in leprosy. An experimental and clinical study. *Lancet* 1964;ii:673-4.
- ⁷ Rees RJW, Waters MFR, Weddell AGM, Palmer E. Experimental lepromatous leprosy. *Nature* 1967;**215**:599-602.
- ⁸ Waters MFR, Rees RJW, McDougall AC, Weddell AGM. Ten years of dapsone in lepromatous leprosy: clinical, bacteriological and histological assessment and the finding of viable leprosy bacilli. *Lepr Rev* 1974;**45**:288-98.
- ⁹ Rees RJW, Waters MFR, Pearson JMH, Helmy HS, Laing ABG. Long-term treatment of dapsone-resistant leprosy with rifampicin: Clinical and bacteriological studies. *Int J Lepr* 1976;**44**:159-69.
- ¹⁰ Waters MFR, Rees RJW, Pearson JMH, Laing ABG, Helmy HS, Gelber RH. Rifampicin for lepromatous leprosy: nine years' experience. *Br Med J* 1978;ii:133-6.
- ¹¹ Feldman R, Sturdivant M. Leprosy in the US, 1950-1969: an epidemiologic review. *South Med J* 1976;**69**:970-9.
- ¹² Shepard CC. Acid-fast bacilli in nasal excretions in leprosy, and results of inoculation of mice. *Am J Hyg* 1960;**71**:147-57.
- ¹³ Shepard CC, Levy L, Fasal P. The death of *Mycobacterium leprae* during treatment with 4,4'-diaminodiphenylsulfone (DDS). Initial rate in patients. *Am J Trop Med Hyg* 1968;**17**:769-75.
- ¹⁴ Levy L, Shepard CC, Fasal P. Clofazimine therapy of lepromatous leprosy caused by dapsone-resistant *Mycobacterium leprae*. *Am J Trop Med Hyg* 1972;**21**:315-21.
- ¹⁵ Rees RJW, Pearson JMH, Waters MFR. Experimental and clinical studies on rifampicin in treatment of leprosy. *Br Med J* 1970;ii:89-92.
- ¹⁶ Shepard CC, Levy L, Fasal P. Rapid bactericidal effect of rifampicin on *Mycobacterium leprae*. *Am J Trop Med Hyg* 1972;**21**:446-9.
- ¹⁷ Jacobson RR, Hastings RC. Rifampicin-resistant leprosy. *Lancet* 1976;ii:1304-5.
- ¹⁸ World Health Organisation. *WHO expert committee on leprosy. Fifth report*. Technical Report Series No 607. Geneva: WHO, 1977:25.
- ¹⁹ Godal T, Myklestad B, Samuel DR, Myrvang B. Characterisation of the cellular immune defect in lepromatous leprosy: a specific lack of circulating *Mycobacterium leprae* reactive lymphocytes. *Clin Exp Immunol* 1976;**9**:821-31.
- ²⁰ Kirchheimer WF, Storrs EH. Attempts to establish the armadillo (*Dasypus novemcinctus* Linn) as a model for the study of leprosy. 1. Report of lepromatoid leprosy in an experimentally infected armadillo. *Int J Lepr* 1971;**39**:693-702.
- ²¹ World Health Organisation. *Report of the IMMLEP subcommittee meeting on the planning of leprosy vaccine trials, Geneva, 12-14 February 1980*. Geneva: WHO, 1980. (TDR/IMMLEP (SUB-TRIALS)/80.3.)
- ²² World Health Organisation. *Report of the fifth meeting of the scientific working group on the immunology of leprosy (IMMLEP), Geneva, 24-26 June 1980*. Geneva: WHO, 1980. (Annex 4. TDR/IMMLEP-SWG(5)/80.3.)
- ²³ World Health Organisation. *Report of the third meeting of the scientific working group (SWG) on the chemotherapy of leprosy (THELEP), Geneva, 20-22 October 1980*. Geneva: WHO, 1981. (TDR/THELEP-SWG(3)/80.3.)
- ²⁴ World Health Organisation. *Report of the ninth meeting of the steering committee of the scientific working group on the chemotherapy of leprosy (THELEP), Geneva, 8-10 April 1981*. Geneva: WHO, 1981. (TDR/THELEP-SC(9)/81.3.)
- ²⁵ World Health Organisation. *WHO expert committee on leprosy. Fourth report*. Technical Report Series No 459. Geneva: WHO, 1970.

Medicine and Books

Harsh words on the penal system

Criminal Welfare on Trial: Cases for Contraction? No 1. Colin Brewer, Terence Morris, N K Patricia Morgan, and Maurice North. (Pp 95; £2.65.) The Social Affairs Unit. 1981.

The Social Affairs Unit seems to be a collection of enthusiastic monetarists who are arguing for less public expenditure in social welfare. They aim at producing a series of pamphlets subtitled "Cases for Contraction?" In his preface to the first, *Criminal Welfare on Trial*, Dr Digby Anderson, the unit's director, sounds shocked to discover that "Law" turns out to be about welfare as well as offences. Enforcement turns out to be about therapy as well as punishment or deterrence. Both turn out to employ social workers and therapists as well as judges and policemen."

Collectively the four authors have some harsh and occasionally incorrect things to say about our penal system. Professor Maurice North is honest enough to admit that his contribution is "a counsel of despair." The sacred cows that are to be led to the slaughterhouse include "the medical model," psychotherapy, the Parole Board, "executive justice," the Children and Young Persons Act 1969, the Labour Party, probation, imprisonment, intermediate treatment for young offenders, social work, psychiatry, Marxism, and so on. At the end of this iconoclastic orgy we are left with very few alternative proposals. Brewer advocates a "benevolent Gulag" for the habitual drunken offender or better still compulsory Antabuse given as a condition of probation—all this at the end of a chapter arguing against the involvement of psychiatry in the treatment of offenders. Morris argues more convincingly for the abolition of the Parole Board (although he gets his figures about the

Board's impact on the prison population hopelessly wrong) but falters at the end and advocates instead the resentencing of offenders after one-third of the original sentence has been served, the Parole Board being preserved to argue against the release of individuals if they feel that is appropriate. He fails to distinguish, at any point in his chapter, between the functions of the Parole Board for prisoners on fixed sentences and those on indeterminate or life sentences. Morgan wants us to go "back to justice," to repeal the Children and Young Persons Act and to punish children appropriately for their crimes. She argues that, "Crime without punishment is a nonsense" and that rehabilitative systems destroy legal rights and spawn injustices. She is clearly stronger on causes than remedies, for she knows that "the main reason for the increase in recidivism following prison or Approved School over the last couple of decades lies in the fact that society is more conducive to law breaking than it was in the past or, conversely, that countervailing pressures against delinquency and crime are now weaker than at any time this century." North simply reckons that prisons are ineffective and overcrowded. He believes that probation is also pretty ineffective but has the virtue of being cheap and could be made cheaper by diluting the dose for each individual offender. He throws up his hands, declaring that, "A nation in decline like our own, with a moribund industry and a constitution that is cracking up, is not likely to find solutions to social problems anymore than it is likely to find solutions to industrial, economic, or political ones."

The problem I found with this pamphlet was that it irritated me so much with its prejudices and its arguments from false premises, that the serious matters it is trying to bring forward